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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/717,845	11/19/2003	Ruth A, Gjerset	049146-1001	9478

30542 7590 02/13/2007

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EXAMINER	
PRIEBE, SCOTT DAVID	
ART UNIT	PAPER NUMBER
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/13/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/717,845	GJERSET ET AL.	
	Examiner	Art Unit	
	Scott D. Priebe, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15,17-22,24-29 and 31-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15,17-22,24-29,31-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 1/17/2007 has been entered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

Claims 15, 17-22, 24-29, and 31-35 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record set forth in the Office action of 7/28/05. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's arguments filed 1/17/05 have been fully considered but they are not persuasive. The amendment to the claims overcomes the grounds of rejection relating to new matter set forth in the Office action of 3/17/06, but not the original grounds of rejection from the Office action of 7/28/05, nor does Applicant provide any arguments in response to the original

grounds of rejection. Deletion of both occurrences of "or a variant thereof" from claims 15 would overcome this rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 15, 17, 19, 20, 22, 24, 26, 28, 29, 31, 33, and 35 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Teimann, WO 01/11063, an English translation of which has been provided.

Tiemann describes bicistronic viral vectors, e.g. retrovirus or AAV, and non-viral vectors for the treatment of malignant or metastatic cancers, e.g. of liver, breast, lung, skin (melanoma), or prostate, comprising coding sequence for p53 and p14ARF under control of a single promoter and separated by an IRES; and use of same (i.e. as a pharmaceutical composition) in treating cancers. See entire reference, especially, in the translation, at pages 8-12, and claims 1, 3, 17-19, and 22-28.

Claim Rejections - 35 USC § 103

Claims 15, 17-22, 24-29, and 31-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roth et al., US 5,747,469 in view of: either or both of Lu et al. (Cancer Res.

62: 1305-1310, 01 March 2002) or Tango et al. (Hum. Gene Ther. 13: 1373-1382, 20 July 2002); Almond et al., WO 99/47690; and Teimann, WO 01/11063.

Roth describes viral vectors, such as retrovirus, adenovirus, AAV, HSV, or CMV vectors, or non-viral vectors in liposomal formulations, that express p53, and methods of treating tumors or cancer in an individual, such as skin, lung, and breast cancer by administration of the vector to tumors and also treating the patient with chemotherapy or radiation therapy. See entire document, especially the claims. Roth does not teach including a p14ARF gene on the vector, i.e. a bicistronic construct or vector.

However, Lu disclosed that tumors without a p53 mutation are often resistant to p53 gene therapy (page 1305). Lu disclosed that a major factor in the resistance to p53 gene therapy involving p53+ tumor cells is likely to be loss of ARF expression in the p53+ tumor cells and the resultant inhibition and increased degradation of p53 mediated by MDM2, whose expression is induced by p53, and which is inhibited by ARF (page 1307, col. 2). Lu showed that co-transfection with separate vectors encoding p14ARF and p53 was significantly more effective at inducing cell death in tumor cell lines (page 1306). Lu taught that co-expression of p53 with ARF in gene therapy will be more effective for tumors that have p53+ tumor cells (page 1309, col. 1).

Also, Tango disclosed that co-transfection of tumor cells both *in vitro* and *in vivo* with vectors (administered simultaneously) expressing p14ARF (the human homolog of the mouse p19ARF) and p53 greatly enhances the tumoricidal effect of either p53 or ARF gene therapy alone as ectopic expression of ARF enhances the effectiveness of p53 gene therapy. Like Lu,

Tango taught that ARF inhibits MDM2, which then reduces or eliminates increased degradation of p53. See entire document, especially pages 1380-1381.

Neither Lu nor Tango suggests including both the p53 and p14ARF genes on a bicistronic construct or vector.

However, Almond et al. generally describes the treatment of cancer with two or more genes at the same time, which augments the action of one or both genes. It teaches that the use of separate vectors, each encoding a different therapeutic gene, presents a variety of problems including immunogenicity, oncogenicity, and reduced transduction efficiency (page 3). Almond discloses that these problems can be reduced by introducing both therapeutic genes, e.g. including a p53 gene, on a single vector, such as an adenovirus, AAV, herpesvirus, or retrovirus vector or in a liposome, which ensures that both genes are expressed in the same cells. The genes may either be present in the vector in separate expression cassettes, i.e. each under control of a different promoter, or they can be present in a single expression cassette under control of the same promoter with an IRES separating the genes. (See pages 4-10, 84 for overview). Almond also teaches that the multi-gene therapy can be combined with radiation therapy or chemotherapy (page 91).

More specifically, Tiemann describes bicistronic viral vectors, e.g. retrovirus or AAV, and non-viral vectors for the treatment of malignant or metastatic cancers, e.g. of liver, breast, lung, skin (melanoma), or prostate, comprising coding sequence for p53 and p14ARF under control of a single promoter and separated by an IRES; and use of same (i.e. as a pharmaceutical composition) in treating cancers. See entire reference, especially, in the translation, at pages 8-

12, and claims 1, 3, 17-19, and 22-28. Tiemann also discloses that treating tumor cells with both p53 and p14ARF genes synergistically kills tumor cells.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have included a p14ARF gene on the vector of Roth, either under control of the same promoter as the p53 gene with an IRES between the p53 and ARF genes, or under control of a different promoter than that of the p53 gene, as generally suggested by Almond for treating cancer with two or more transgenes and specifically suggested by Tiemann with respect to p53 and p19ARF. One would have been motivated to include the p14ARF gene because Lu and Tango taught that co-expression of p14ARF with p53 improved the effectiveness of the p53 by blocking the inhibitory effects of MDM2 on p53, and Tiemann taught that this transgene combination was synergistic. Lu, Tango, and Tiemann taught that the combination would be more effective than p53 gene therapy alone. From the teachings of Almond and Tiemann, one would have been motivated to include both the p53 and p14ARF genes on the same vector to avoid the problems associated with using separate vectors in gene therapy, and to improve the efficiency of the gene therapy, and under control of a single promoter, since both Almond and Tiemann showed that this was an art accepted vector design for expressing multiple transgenes targeting cancer cells.

Applicant's arguments filed 1/17/05 have been fully considered but they are not persuasive. The subsequently uncovered Tiemann reference has been added to the grounds of rejection to show that in fact those of skill in the art had described including both p53 and p14ARF genes on a single vector under control of the same promoter for the purpose of treating cancer with this synergistic transgene combination, and that doing so was an obvious variation of

using two separate vectors as in Lu and Tango. Almond is mischaracterized in the arguments as teaching to use a single vector when there is a problem with immunogenicity, oncogenicity or reduced transduction efficiency, rather Almond teaches that these are problems associated with using multiple vectors to deliver multiple transgenes *in vivo*, which are reduced by using a single vector comprising the transgenes. Applicant reiterates their arguments alleging unexpected results, but these arguments have already been addressed.

Double Patenting

Applicant remains advised that should claims 22 and 24-28 be found allowable, claims 29 and 31-35, respectively, will be objected to under 37 CFR 1.75 as being a substantial duplicates thereof. Applicant's arguments filed 1/17/05 have been fully considered but they are not persuasive. Applicant argues that the consequences of the treatments recited in the preambles of claims 22 and 29 are very different and therefore the claims have different scope. In response, there is no material or procedural difference evident between the methods of claims 22 and 29, and no evidence of record that this single recited method does not result in all of the consequences recited in claims 22 and 29, i.e. some tumor cells simply stop dividing and others are killed. Simply because one can write two claims differing by reciting different outcomes of the same method, does not mean they describe different methods or methods of differing scope. Applicant asserts that the methods have different scope but does not provide any evidence or indication of just what would be different about the scopes of these two sets of claims or identify a single embodiment or species readable on one claim that is not also readable on the other.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe, Ph.D. whose telephone number is (571) 272-0733. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D. can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Scott D. Priebe, Ph.D.
Primary Examiner
Art Unit 1633